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Mild Ruthenium-Catalyzed Intermolecular Alkyne Cyclotrimerization

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Abstract: Grubbs' catalyst [$(PCy_3)_2Cl_2Ru$=CHPh, **7**] was shown for the first time to be an effective catalyst for the mild intermolecular cyclotrimerization of terminal alkynes (**1-6**). The reaction is general and the isomeric trisubstituted benzene derivatives (**8-13**) were isolated in good to excellent yields.
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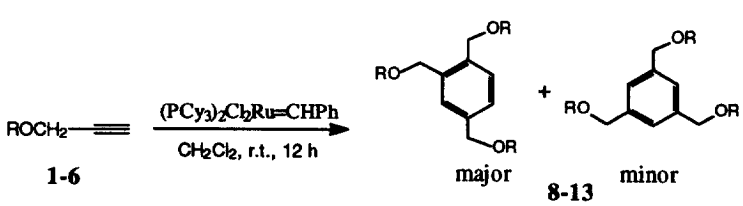
Metal-catalyzed cyclotrimerization of an alkyne is one of the most powerful methods for the assembly of highly substituted benzene derivatives. It has been found that several reactive organometallic reagents (e.g., Co,[1] Pd,[2] Cr,[3] Ni,[4] Rh[5] and Ta[6]) have been used for this transformation. Despite the fact that all these transition metals are useful in intramolecular cyclotrimerization, many difficulties are encountered in intermolecular cyclotrimerization reactions. Although, Blechert and his co-workers have recently shown that triynes can undergo a cascade of four metathesis reactions[7] to provide the corresponding benzene derivatives using Grubbs'catalyst **7**,[8] until now no example has been reported for intermolecular cyclotrimerization reactions using bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (**7**).

In view of the important role of multivalent carbohydrate derivatives in glycobiology,[9] we recently initiated a program toward the synthesis of carbohydrate-containing clusters utilizing olefin self-[10] or cross-[11] metathesis reactions using **7** and various other transition metals. Under olefin metathesis conditions, carbohydrate homodimers[10] and glycopeptoids[11] were successfully synthesized from O- or C-allyl glycopyranosides using catalyst **7**. Based on initial Blechert's observations[7] and the successful palladium(0)-catalyzed cross-couplings transformations of 2-propynyl glycosides under Sonogashira conditions,[12] it was also deemed of interest to evaluate the behavior of these unexploited glycosides under metathesis conditions in the presence of catalyst **7**. Interestingly, it was found that treatment of 2-propynyl α-D-mannopyranoside **1** can undergo cyclotrimerization reaction in the presence of Grubbs' catalyst to give a mixture of regioisomeric aryl mannosides **8** (Scheme 1). As oligosaccharide mimetics, such molecules may find biological utility as "cluster-type ligands" and may help to elucidate binding specificity of multiple carbohydrate-protein interactions.[9] Herein, we report the first Grubbs'-catalyzed intermolecular cyclotrimerization of 2-propynyl derivatives in good yields.



1-6 **8-13**

Scheme 1

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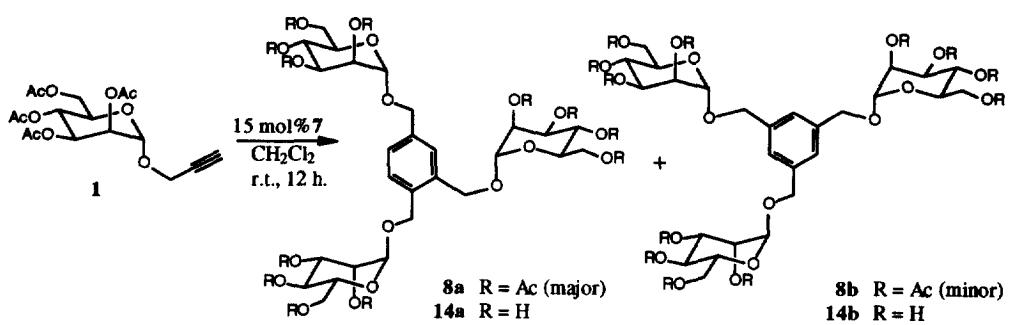
The starting material, peracetylated 2-propynyl α-D-mannopyranoside (**1**) was synthesized under boron trifluoride diethyl etherate catalyzed glycosylation reaction between peracetylated D-mannopyranose and freshly distilled propargyl alcohol.[13] Compound **1** was then treated with Grubbs' catalyst **7** (15 mol%) in dry dichloromethane at room temperature for 12 h. The desired trisubstituted benzene derivatives **8a,b** were isolated as a mixture of 1,2,4- (**8a**) and 1,3,5-(**8b**) regioisomers in 75 % yield (Scheme 2). The reaction was found to be highly regioselective in favored of the 1,2,4-regioisomer **8a** over that of **8b** (90:10). The reaction is similar in its outcome to that previously observed[14] in analogous transformations involving dicobalt octacarbonyl ($Co_2(CO)_8$).[15] The regioisomeric structures and the ratio were determined from the ^{1}H-NMR spectra and the data reported in the literature.[14] For instance, the aromatic protons for the 1,2,4-isomer **8a** appeared at δ 7.36 ppm (d, J=7.8 Hz), 7.31 (dd, J=7.8, 1.5 Hz) and 7.29 (d, J=1.5 Hz) and for the symmetrical 1,3,5-isomer **8b** as a singlet at δ 7.24 ppm. The ^{13}C-NMR showed aromatic carbon signals at 136.7, 135.0, 134.8 (quaternary carbons) and 130.0, 129.3 and 128.1 ppm (tertiary carbons) for the 1,2,4-isomer and those for the 1,3,5-isomer appeared at 137.1 ppm (quaternary carbons) and at 127.4 ppm (tertiary carbons). It is noteworthy to mention that other transition metals, such as Wilkinson catalyst[5] or $Pd(PPh_3)_4$,[16] failed to provide such trimers.

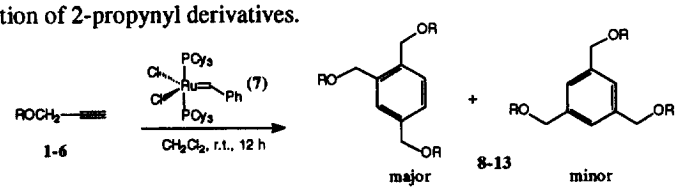
To further explore the scope and generality of this reaction, we prepared 2-propynyl β-D-galactopyranoside (**2**) and 2-propynyl β-D-lactopyranoside (**3**) according to the same procedure reported for compound **1** (Et_2O-BF_3, propargyl alcohol). Thus, treatment of **2** and catalyst **7** gave the corresponding benzene trimer **9** in 72 % yield (Table 1). The regioisomeric ratio (1,2,4 and 1,3,5) was found to be 9:1 from the ^{1}H-NMR spectrum. Although, the reaction between **3** and catalyst **7** was somewhat slower at room temperature, it proceeded smoothly when the reaction mixture was heated at 40°C for 6 h. The cyclotrimerized product **10** was isolated in 66 % yield with the same regioisomer ratio.

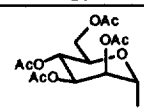
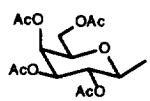
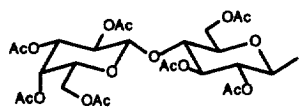
Encouraged by the generality and scope of the cyclotrimerization method for the synthesis of aromatic cluster glycosides, we evaluated the possibility of applying this methodology to simple 2-propynyl derivatives with the intention to generate core structures onto which a wide range of carbohydrate derivatives could be added at a later stage. For that purpose, compounds **4**, **5** and **6** were prepared.



Scheme 2

Table 1. Cyclotrimerization of 2-propynyl derivatives.



Entry	Substrate	R	Product	Yield	Isomer Ratios
1	1		8	75	90:10
2	2		9	72	90:10
3	3		10	66	90:10
4	4	Ac	11	70	95:5
5	5	TBDMS	12	82	75:25
6	6	Piv	13	81	95:5

When the above conditions were applied to propynyl acetate **4**, the cyclotrimerization proceeded successfully and gave **11** in 70% yield (1,2,4- and 1,3,5- regioisomers; 95:5). Both regioisomers were unambiguously characterized by comparison with authentic samples.[17] The chemical shifts and coupling patterns of all protons and carbons agreed well for both regioisomers. In a similar manner, propynyl silyl ether **5** and propynyl pivalate **6** reacted with catalyst **7** and gave the corresponding benzene trimers **12** and **13** in 82 and 81% yields, respectively (Table 1).[18-19] The mechanism for this novel intermolecular cyclotrimerization is likely originating from a cascade of four metathesis reactions as previously proposed for the intramolecular version.[7] Catalyst **7** was found to be a living catalyst since it could initiate either a novel cyclotrimerization or even an olefin self-metathesis[10] at the end of the reaction cycle. After transformation of **1** into **8** was completed, catalyst **7** still triggered formation of **13** from **6**.

In conclusion, this methodology expands the scope and versatility of Grubbs' catalyst toward acetylene cyclotrimerization. The potential usefulness of the above carbohydrate clusters was established by deacetylation of compound **8** under Zemplén conditions (MeONa, MeOH, quantitative) to afford water-soluble trimannoside **14a,b** which was shown in preliminary experiments to act as protein cross-linker by forming insoluble cross-linked lattices in the presence of the tetravalent plant lectin, concanavalin A. The biochemical results will be published in due course.

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17. Cochrane, W. P.; Pauson, P. L.; Stevens, T. S. *J. Chem. Soc. (C)* **1968**, 630. Trimethylbenzene-1,3,5- and -1,2,4-tricarboxylates were reduced with $LiAlH_4$ to give the corresponding triols, which upon acetylation (Ac_2O, pyridine) gave the two regioisomers.
18. **General cyclotrimerization procedure**: To a solution of compound **1** (100 mg, 0.259 mmol) in dry CH_2Cl_2 (1 mL) was added Grubbs'catalyst **7** (11 mg, 15 mol %). After stirring for 12 h at room temperature, the solvent was evaporated to dryness and the crude mixture was purified by silica gel column chromatography (ethyl acetate: hexane; 3:2) to provide **8** (75 mg, 75 % yield) (1,2,4 and 1,3,5 regioisomers; 90:10).
19. All compounds were fully characterized by ^1H, ^{13}C NMR and mass spectral data. **Compound 9:** ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.30 (d, J = 7.8 Hz, 1H, H-Ar), 7.23 (s, 1H, H-Ar), 7.20 (dd, J = 1.5, 7.8 Hz, H-Ar), 7.15 (s, 1H, H-Ar for the sym. isomer); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 137.4, 126.6 (Ar for sym. isomer), 136.8, 134.9, 134.9, 128.8, 128.2, 127.4 (Ar), 100.0 (C-1),70.9 (C-3), 68.9 (C-5), 68.3 (C-2), 67.0 (benzylic), 61.2 (C-6). MS(FAB) *m/z*: 1198.4011 (M+K). **Compounds 10:** ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.25 (d, J = 7.0 Hz, 1H, H-Ar), 7.18 (bs, 1H, H-Ar), 7.17 (bd, J = 7.0 Hz, 1H, H-Ar), 7.10 (s, 1H, H-Ar for sym. isomer), 5.31 (dd, J = 0.8, 3.4 Hz, 3H, H-4'); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 137.4, 126.4 (Ar for sym. isomer), 136.9, 135.1, 134.7, 128.8, 128.0, 127.3 (Ar). MS(FAB) m/z: 2063.4721 (M+K). **Compound 11**: ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37 (d, J = 7.8 Hz, 1H, H-Ar), 7.36 (bs, 1H, H-Ar), 7.32 (bd, J = 7.8 Hz, 1H, H-Ar), 7.30 (s, 1H, H-Ar for sym. isomer), 5.16, 5.15, 5.07 (3s, 6H, H-benzylic); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 170.7, 170.5 (CO), 136.8, 127.7 (Ar for sym. isomer), 136.6, 134.8, 134.5, 130.0, 129.4, 128.3 (Ar), 65.6, 66.5, 63.5, 63.4 (benzylic). MS(FAB) *m/z*: 333.1600 (M+K). **Compound 12**: ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38 (bs, 1H, H-Ar), 7.35 (d, J = 7.5 Hz, 1H, H-Ar), 7.22 (bd, J = 7.5 Hz, 1H, H-Ar), 7.20 (s, 1H, H-Ar for sym. isomer); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 141.3, 122.4 (Ar for sym. isomer), 140.1, 138.2, 136.7, 126.6, 124.6, 124.4 (Ar), 65.0, 65.0, 62.8, 62.8 (benzylic). MS(FAB) *m/z*: 511.3842 (M+1). **Compound 13**: ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35 (d, J = 7.9 Hz, 1H, H-Ar), 7.34 (bs, 1H, H-Ar), 7.27 (bd, J =7.9 Hz, 1H, H-Ar), 7.25 (s, 1H, H-Ar for sym. isomer), 5.16, 5.15, 5.08 (3s, 6H, H-benzylic); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 178.2, 178.0 (2x)(CO), 137.2, 126.2 (Ar sym. isomer), 136.7, 134.9, 134.2, 129.1, 128.5, 127.3 (Ar), 65.5, 65.4, 63.5, 63.5 (benzylic). MS(FAB) *m/z*: 421.2396 (M+1).